selective for only the TCN and doesn't significantly affect the many other sensory nerves that provide normal tactile sensations and "cutaneous awareness." Since lidocaine and other topical local anesthetics lack this specificity for TCN, they can cause numbness and loss of function.

[0005] While topically applied strontium can rapidly inhibit the activation of TCN sensory nerve subsets that transmit sensations of pain (*e.g.,* burning and stinging) and pruritus (itching), recent investigations to understand strontium's anti-irritant mechanisms surprisingly reveal that strontium also has negative effects on several biochemical pathways that tend to negate the positive anti-irritant benefits of strontium for treatment of neuropathic conditions.

[0006] Therefore it is desirable to create new strontium-containing molecules, complexes and formulations that increase the "positive" therapeutic benefits of strontium and decrease the "negative" effects of strontium on acute pain, pruritis and neuropathic conditions

SUMMARY ~~OF THE INVENTION~~

[0007] In accordance with the teachings herein, the present disclosure relates generally to compositions of strontium-containing complexes in a suitable carrier vehicle.

In a first aspect, there is provided a composition comprising a complex of: divalent cationic strontium; at least one cysteine-based anti-oxidant selected from the group consisting of: cystine, N-acetyl cysteine (NAC), N-acetyl cysteinate, N-acetyl cystine, N,S-diacetylcysteine, and esters thereof; and at least one polyhydroxyphenol selected from the group consisting of: gallic acid, caffeic acid, quercetin, luteolin, epigallocatechin gallate, epigallocatechin, epicatechin gallate, genistein, myricetin, and esters thereof; in a suitable carrier vehicle.

In a second aspect, there is provided a composition comprising a complex of: divalent cationic strontium; andat least one polyhydroxyphenol selected from the group consisting of: gallic acid, caffeic acid, quercetin, luteolin, epigallocatechin gallate, epigallocatechin, epicatechin gallate, genistein, myricetin, and esters thereof; in a suitable carrier vehicle.

In a third aspect, there is provided a composition comprising a complex of:

divalent cationic strontium; and at least one cysteine-based anti-oxidant selected from the group consisting of: cystine, N-acetyl cysteine (NAC), N-acetyl cysteinate, N-acetyl cystine, N,S-diacetylcysteine, and esters thereof; in a suitable carrier vehicle.

[0008] The complexes are bipartite or tripartite in nature, in that they include at least one or two different components: divalent cationic strontium, and at least one counterion, such as a polyhydroxyphenol or an aromatic amino acid. In the form of a tripartite composition, the complexes include divalent cationic strontium, at least one polyhydroxyphenol, and at least one cysteine-based antioxidant.

[0009] The cysteine-based anti-oxidant may be selected from the group consisting of: cysteine, cystine, N-acetyl cysteine (NAC), N-acetyl cysteinate, N-acetyl cystine and N,S-diacetylcysteine, or mixtures thereof.

[0010] In addition, the polyhydroxyphenol may be selected from the group consisting of: gallic acid, caffeic acid, quercetin, luteolin, epigallocatechin gallate, epigallocatechin, epicatechin gallate, genistein and myricetin, or mixtures thereof. In

one embodiment the polyhydroxyphenol is a mixture of gallic acid and caffeic acid.

[0011] Either the bipartite or tripartite complexes may also be complexed with a polymer, such as a polyanionic polymer. This polymer may be s selected from the group consisting of: polyvinylpyrrolidone (PVP), cyclodextrins, carragenans, alginic acid, xanthan gum, sulfated polysaccharides, pentosan polysulfate, chondroitin sulfate, dextran sulfate and heparin sulfate.

[0012] The osmolarity of the compositions may beneficially have high osmotic acitivity, such as having an osmolarity equal to or greater than 400 mOsm, or between 400 and 2000 mOsm.

[0013] The polyhydroxyphenol(s) is(are) in essentially pure form when added to the compositions described herein, or is(are) added in the form of a plant extract, such as green tea or soy extract.

[0014] In an alternate embodiment of a tripartite composition, the at least one cysteine-based anti-oxidant and the at least one polyhydroxyphenol are conjugated together by a cleavable bond, such as a peptide bond, an ester bond, a thioester bond, an enzymatically cleavable bond, a disulphide bond, or a pH dependent bond.

[0015] In an alternate embodiment of a bipartite composition, the divalent cationic strontium is complexed with at least one polyhydroxyphenol (as described above), and the complex is placed in a suitable carrier vehicle prior to administration.

[0016] In yet another embodiment of the bipartite composition, the divalent cationic strontium is complexed with an aromatic amino acid, and the complex is placed in a suitable carrier vehicle prior to administration. Such amino acids include, for example, histidine, tyrosine, phenylalanine and tryptophan, and are in one embodiment in the L isomer form.

[0017] The compositions containing bipartite complexes can also include other constituents, such as any of the aforementioned strontium counterions.

In a fourth aspect, there is provided the use of the compound of the first aspect in the manufacture of a medicament for treating acute pain or pruritus in a subject.

In a fifth aspect, there is provided the use of the compound of the first aspect in the manufacture of a medicament for treating chronic pain or pruritus in a subject.

In a sixth aspect, there is provided the use of the compound of the first aspect in the manufacture of a medicament for treating neuropathic pain or pruritus in a subject.

In a seventh aspect, there is provided the use of the compound of the second aspect in the manufacture of a medicament for treating pain or pruritus in a subject.

In an eighth aspect, there is provided the use of the compound of the third aspect in the manufacture of a medicament for treating pain or pruritus in a subject.

[0018] Other ~~aspects~~ embodiments of the ~~invention~~ present disclosure are found throughout the specification.

CLAIMS

1. A composition comprising a complex of:

divalent cationic strontium;

at least one cysteine-based anti-oxidant selected from the group consisting of: cystine, N-acetyl cysteine (NAC), N-acetyl cysteinate, N-acetyl cystine, N,S-diacetylcysteine, and esters thereof; and

at least one polyhydroxyphenol selected from the group consisting of: gallic acid, caffeic acid, quercetin, luteolin, epigallocatechin gallate, epigallocatechin, epicatechin gallate, genistein, myricetin, and esters thereof;

in a suitable carrier vehicle.

2. The composition according to claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof.

3. The composition according to claim 1, wherein the at least one polyhydroxyphenol is gallic acid or esters thereof.

4. The composition according to claim 1, wherein the at least one polyhydroxyphenol is a mixture of gallic acid and caffeic acid, or esters thereof.

5. The composition according to claim 1, further comprising a polymer.

6. The composition according to claim 5, wherein the polymer is a polyanionic polymer.

7. The composition according to claim 5, wherein the polymer is selected from the group consisting of: polyvinylpyrrolidone (PVP), cyclodextrins, carrageenan, alginic acid, xanthan gum, sulfated polysaccharides, pentosan polysulfate, chondroitin sulfate, dextran sulfate and heparin sulfate.

~~8-9. (Canceled)~~

~~10~~8. The composition according to claim 1, wherein the at least one polyhydroxyphenol is added to the composition as a plant extract.

~~11~~9. The composition according to claim ~~10~~8, wherein the plant extract is a green tea extract or a soy extract.

~~12~~10. The composition according to claim 1, wherein the at least one cysteine-based anti-oxidant and the at least one polyhydroxyphenol are conjugated together by a cleavable bond.

~~13~~11. The composition according to claim ~~12~~10, wherein the cleavable bond is selected from the group consisting of: a peptide bond, an ester bond, a thioester bond, an enzymatically cleavable bond, a disulphide bond, and a pH dependent bond.

~~14~~12. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof.

~~15~~13. The composition of claim 1, wherein the at least one polyhydroxyphenol is caffeic acid or esters thereof.

~~16~~14. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof.

~~17~~15. The composition of claim 1, wherein the at least one polyhydroxyphenol is myricetin or esters thereof.

~~18~~16. The composition of claim 1, wherein the at least one polyhydroxyphenol is a mixture of gallic acid, caffeic acid, and myricetin, or esters thereof.

~~19~~17. A composition comprising a complex of:

divalent cationic strontium; and

at least one polyhydroxyphenol selected from the group consisting of: gallic acid, caffeic acid, quercetin, luteolin, epigallocatechin gallate, epigallocatechin, epicatechin gallate, genistein, myricetin, and esters thereof;

in a suitable carrier vehicle.

~~20~~18. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is gallic acid or esters thereof.

~~21~~19. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is a mixture of gallic acid and caffeic acid, or esters thereof.

~~22~~20. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is a mixture of gallic acid, caffeic acid, and myricetin, or esters thereof.

~~23. (Canceled)~~

~~24~~21. The composition of claim 1, further comprising at least one aromatic amino acid selected from the group consisting of: histidine, tyrosine, phenylalanine and tryptophan.

~~25~~22. The composition of claim ~~24~~21, wherein the at least one aromatic amino acid is an L isomer.

~~26. (Canceled)~~

~~27~~23. The composition of claim 1, wherein the at least one polyhydroxyphenol is a mixture of gallic acid and myricetin, or esters thereof.

~~28-30. (Canceled)~~

~~31~~24. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is a mixture of gallic acid and myricetin, or esters thereof.

~~32~~25. The composition of claim 1, wherein the at least one polyhydroxyphenol is genistein or esters thereof.

~~33~~26. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof and the at least one polyhydroxyphenol is gallic acid or esters thereof.

~~34~~27. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof and the at least one polyhydroxyphenol is gallic acid or esters thereof.

~~35~~28. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof and the at least one polyhydroxyphenol is gallic acid or esters thereof.

~~36~~29. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof and the at least one polyhydroxyphenol is caffeic acid or esters thereof.

~~37~~30. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof and the at least one polyhydroxyphenol is caffeic acid or esters thereof.

~~38~~31. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof and the at least one polyhydroxyphenol is caffeic acid or esters thereof.

~~39~~32. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof and the at least one polyhydroxyphenol is myricetin or esters thereof.

~~40~~33. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof and the at least one polyhydroxyphenol is myricetin or esters thereof.

~~41~~34. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof and the at least one polyhydroxyphenol is myricetin or esters thereof.

~~42~~35. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof and the at least one polyhydroxyphenol is genistein or esters thereof.

~~43~~36. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof and the at least one polyhydroxyphenol is genistein or esters thereof.

~~44~~37. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof and the at least one polyhydroxyphenol is genistein or esters thereof.

~~45~~38. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof and the at least one polyhydroxyphenol is a mixture of gallic acid and caffeic acid, or esters thereof.

~~46~~39. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof and the at least one polyhydroxyphenol is a mixture of gallic acid and caffeic acid, or esters thereof.

~~47~~40. The composition of claim 1, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof and the at least one polyhydroxyphenol is a mixture of gallic acid and caffeic acid or esters thereof.

~~48~~41. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is caffeic acid or esters thereof.

~~49~~42. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is myricetin or esters thereof.

~~50~~43. The composition of claim ~~19~~17, wherein the at least one polyhydroxyphenol is genistein or esters thereof.

~~51~~44. The composition of claim ~~19~~17, further comprising an aromatic amino acid selected from the group consisting of histidine, tyrosine, phenylalanine, and tryptophan.

~~52~~45. The composition of claim ~~51~~44, wherein the aromatic amino acid is an L-isomer.

~~53~~46. The composition of claim ~~19~~17, further comprising a polymer.

~~54~~47. The composition of claim ~~53~~46, wherein the polymer is a polyanionic polymer

~~55~~48. The composition of claim ~~53~~46, wherein the polymer is selected from the group consisting of: polyvinylpyrrolidone (PVP), cyclodextrins, carrageenan, alginic acid, xanthan gum, sulfated polysaccharides, pentosan polysulfate, chondroitin sulfate, dextran sulfate, and heparin sulfate.

~~56~~49. A composition comprising a complex of:

divalent cationic strontium; and

at least one cysteine-based anti-oxidant selected from the group consisting of: cystine, N-acetyl cysteine (NAC), N-acetyl cysteinate, N-acetyl cystine, N,S-diacetylcysteine, and esters thereof;

in a suitable carrier vehicle.

~~57~~50. The composition of claim ~~56~~49, wherein the at least one cysteine-based anti-oxidant is cystine or esters thereof.

~~58~~51. The composition of claim ~~57~~50, wherein the cystine is L-cystine or esters thereof.

~~59~~52. The composition of claim ~~56~~49, wherein the at least one cysteine-based anti-oxidant is N-acetyl cysteine (NAC) or esters thereof.

~~60~~53. The composition of claim ~~56~~49, wherein the at least one cysteine-based anti-oxidant is N,S-diacetylcysteine or esters thereof.

~~61~~54. The composition of claim ~~56~~49, further comprising a polymer.

~~62~~55. The composition of claim ~~61~~54, wherein the polymer is a polyanionic polymer

~~63~~56. The composition of claim ~~61~~54, wherein the polymer is selected form the group consisting of: polyvinylpyrrolidone (PVP), cyclodextrins, carrageenan, alginic acid, xanthan gum, sulfated polysaccharides, pentosan polysulfate, chondroitin sulfate, dextran sulfate, and heparin sulfate.

~~64~~57. The composition of claim ~~10~~8, wherein the at least one polyhydroxyphenol is myricetin or esters thereof.

~~65~~58. ~~A method of treating acute pain or pruritus in a subject comprising administering~~ Use of the compound of claim 1 in the manufacture of a medicament for treating acute pain or pruritus in a subject~~to the subject~~.

~~66~~59. The ~~method~~ use of claim ~~65~~58, wherein the compound is to be topically administered.

~~67~~60. The ~~method~~ use of claim ~~66~~59, wherein the compound is to be topically administered to keratinized skin or mucous membranes in the eye, mouth, throat, esophagus, gastrointestinal tract, respiratory tract or genitourinary tract.

~~68~~61. The ~~method~~ use of claim ~~65~~58, wherein the acute pain or pruritus is due to allergies, insect bites, exposure to venom, poison ivy, atopic dermatitis, psoriasis, thermal burns, ionizing

radiation, exposure to chemicals, trauma, surgery, nerve compression, oral or throat ulcers, bacteria infections, or viral infections.

~~69~~62. ~~A method of treating chronic pain or pruritus in a subject comprising administering~~ Use of the compound of claim 1 in the manufacture of a medicament for treating chronic pain or pruritus in a subject~~to the subject~~.

~~70~~63. The ~~method~~ use of claim ~~69~~62, wherein the compound is to be topically administered.

~~71~~64. The ~~method~~ use of claim ~~70~~63, wherein the compound is to be topically administered to keratinized skin or mucous membranes in the eye, mouth, throat, esophagus, gastrointestinal tract, respiratory tract or genitourinary tract.

~~72~~65. The ~~method~~ use of claim ~~69~~62, wherein the chronic pain or pruritus is due to atopic dermatitis, psoriasis, viral infections, nerve compression, back pain, amputation, or trauma.

~~73~~66. ~~A method of treating neuropathic pain or pruritus in a subject comprising administering~~ Use of the compound of claim 1 in the manufacture of a medicament for treating neuropathic pain or pruritus in a subject~~to the subject~~.

~~74~~67. The ~~method~~ use of claim ~~73~~66, wherein the compound is to be topically administered.

~~75~~68. The ~~method~~ use of claim ~~74~~67, wherein the compound is to be topically administered to keratinized skin or mucous membranes in the eye, mouth, throat, esophagus, gastrointestinal tract, respiratory tract or genitourinary tract.

~~76~~69. The ~~method~~ use of claim ~~73~~66, wherein the neuropathic pain or pruritus is due to post herpetic neuralgia, back pain, nerve compression, viral infections, multiple sclerosis, Parkinson's disease, diabetes, trauma, amputation, or drug use.

~~77~~70. ~~A method of treating pain or pruritus in a subject comprising administering~~ Use of the compound of claim ~~19~~17 in the manufacture of a medicament for treating pain or pruritus in a subject~~to the subject~~.

~~7871~~. ~~A method of treating pain or pruritus in a subject comprising administering~~ Use of the compound of claim ~~56~~ 49 in the manufacture of a medicament for treating pain or pruritus in a subject~~to the subject~~.